Healthy diets and dietary supplements: recent changes in how we might think about hearing conservation

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INTRODUCTION

Hearing conservation strategies have primarily been targeted at diminishing the level and duration of sound exposure on the person or population of interest, usually through use of environmental engineering or use of personal hearing protection devices (HPDs). Numerous factors limit the application of these two conservation methods--- environmental controls can be limited by cost and technological limits; hearing protection devices can be limited by user compliance and most notably bone/tissue conduction imposed (Berger 2003). Pharmaceutical and/or nutraceutical strategies are therefore of high interest. As the scientific understanding of noise-induced hearing loss (NIHL) has advanced with respect to metabolic pathways activated by noise, age, and ototoxic drugs, such strategies are increasingly likely to succeed, and, importantly, a healthy diet may also prove important. We now know that metabolic stress drives free radical formation, leading to cell death and hearing loss. Three key findings have supported development of novel antioxidant strategies for protection. Free radicals are produced during noise (Yamane et al. 1995; Ohlemiller et al. 1999b); free radical production is long-lasting, with cell death occurring in concert with peak free radical production (Yamashita et al. 2004); and free radical scavengers directly mediate cell death and hearing loss (Yamashita et al. 2005). For detailed discussion of cell death after noise insult, readers are referred to Le Prell et al. (2007b); for detailed update on emerging therapeutics that take advantage of free radical scavenging properties, readers are referred to Le Prell & Bao (2011).

Endogenous protection against free radical insult is mediated via superoxide dismutase (SOD) (Ohlemiller et al. 1999a; Cassandro et al. 2003), catalase (Konings et al. 2007), and glutathione (Usami et al. 1996; Yamasoba et al. 1998), as well as glutathione peroxidase, an enzyme that speeds glutathione reactions (Ohlemiller et al. 2000). The precursors needed for endogenous SOD, catalase, and glutathione production are obtained from dietary sources, suggesting the potential for dietary nutrient intake to importantly influence hearing health, and vulnerability to noise or other insults. This paper focuses on the role of dietary nutrients including vitamins, minerals, and macronutrients (i.e. carbohydrates, fat, and protein) in maintenance of normal hearing and/or prevention of hearing loss. For additional more detailed review, readers are referred to Le Prell and Spankovich (2012).

Vitamins

Vitamin A: Retinol is the non-oxidized form of vitamin A; retinoic acid is the oxidized form. Both pre- (Ahn et al. 2005), and post- (Shim et al. 2009) noise treatment with retinoic acid reduce NIHL; pre-treatment provides better protection than post. ß-carotene is the main source of pro-vitamin A in the diet; it is metabolized to retinol and retinyl esters (i.e., vitamin A) and stored in the liver. When sufficient vitamin A stores exist, metabolism to vitamin A ceases and ß-carotene circulates in plasma. Vitamin A deficiencies increase NIHL (Biesalski et al. 1990), suggesting an important

role for vitamin A in endogenous defense. Indeed, increased serum levels of retinol and pro-vitamin A carotenoids were associated with decreased prevalence of hearing impairment in a community-based epidemiological study in Japan (Michikawa et al. 2009). Dietary sources of vitamin A include liver, milk and cheese; sources of ß-carotene include carrots, spinach, kale, and collard greens (National Institutes of Health Office of Dietary Supplements 2006). There are other carotenoids that are good antioxidants, but which are not sources of vitamin A. One example is lycopene. Lycopene intake was highly correlated with better auditory function in an adult population (Spankovich et al. 2011). Tomato-based products are the primary dietary source of lycopene.

B Vitamins: These include thiamine (B1), riboflavin (B2), niacin (B3), pantothenic acid (B5), pyridoxine (B6), biotin (B7), folic acid/folate (B9), and cobalamin (B12).

Vitamin B9. The natural form of B9 is folate; folic acid is a stable synthetic form (FAO/WHO 2001). Although Berner et al. (2000) reported no relationship between age-related hearing loss (ARHL) and folic acid levels in plasma (Berner et al. 2000), a 3-year study in older adults revealed slower progression of ARHL at low frequencies in subjects receiving folic acid (Durga et al. 2007). Changes were small: 1.0 dB vs 1.7 dB change in PTA at 0.5, 1, and 2 kHz. However, as noted by Dobie (2007), if the changes continued to accrue each year ("a big if"), one might eventually expect a decrease in the proportion of hearing aid candidates at age 75 years. Baseline folate levels in participants were about half the level reported for people living in the US, where folic acid is a normal food additive; the efficacy of supplements may vary in populations with with improved baseline intake. Leafy green vegetables (spinach, turnip greens), citrus fruits and juices, and dried beans and peas are natural folate sources, cereal is a good source of folic acid (National Institutes of Health Office of Dietary Supplements 2009).

Vitamin B12. It is not known whether normal dietary intake of vitamin B12 influences hearing status. However, B12 supplements reduced temporary threshold shift (TTS) in human subjects (Quaranta et al. 2004). B12-treated subjects received 1 mg cyanocobalamin/day x 7 days, followed by a 5 mg dose on the eighth day; controls received placebo injections. Serum B12 was significantly increased, and TTS was decreased at 3 kHz in B12 treated subjects. These doses are greater than can be achieved via diet alone. Beef liver and clams are the best B12 sources; fish, meat, poultry, eggs, milk, and other dairy products, also contain vitamin B12 (National Institutes of Health Office of Dietary Supplements 2010a).

Vitamin C: Unlike virtually all other mammals, humans require dietary vitamin C (Chatterjee 1973; 1975). Vitamin C reduced NIHL in guinea pigs (McFadden et al. 2005). In addition, mice that have been genetically modified such that they cannot synthesize vitamin C have greater ARHL and decreased spiral ganglion cell density compared to wild-type controls, and knock-out mice maintained on high-level vitamin C supplements (Kashio et al. 2009). In human populations, increased intake of vitamin C was linked to improved low-frequency hearing outcomes (Spankovich et al. 2011). Good dietary sources include citrus fruits (oranges, grapefruit) and their juices, red and green peppers, and kiwi; other fruits and vegetables which have vitamin C include broccoli, strawberries, cantaloupe, baked potatoes, and tomatoes (National Institutes of Health Office of Dietary Supplements 2010b).

Vitamin D: Vitamin D was suggested to have a role in auditory function given studies demonstrating compromised auditory function in vitamin D deficient patients. Vitamin D treatment improved hearing thresholds in some, but not all, cases (Brookes & Morrison 1981; Brookes 1983). Vitamin D deficiency has also been linked with prolonged N1 latencies in rats (Ikeda et al. 1987). In mice that lack vitamin D receptors (VDR), threshold sensitivity in young (<6 month), and adult (7-14 month old) mice is equivalent to wild-type mice with vitamin D receptors; however, when aged mice (>15 months old) are compared, VDR mice have worse hearing than age-matched wild-type mice (Zou et al. 2008). Deficits also occur with vitamin D intoxification during aging. The *klotho* mouse does not regulate vitamin D levels, resulting in high serum levels for vitamin D3. *Klotho* mice develope hearing loss at an earlier age than wild type controls, but, maintenance on a vitamin D deficient diet rescues their hearing (Carpinelli et al. 2011). In contrast, a case of a human patient with vitamin D intoxification and existing hearing loss revealed no recovery of hearing even with long-term (20 months) treatment (Allen & Shah 1992). The best sources of vitamin D are fatty fish, such as salmon, tuna, and mackerel; beef liver, cheese, egg yolks, and mushrooms provide small amounts (National Institutes of Health Office of Dietary Supplements 2011). Per that report, while almost all of the U.S. milk supply is vitamin-D fortified, foods made from milk (cheese, ice cream) are not usually fortified.

Vitamin E: Vitamin E is a generic term used to capture all eight members of the tocopherol family. Vitamin E (delivered as synthetic vitamin E, Trolox, or α-tocopherol) reduces NIHL (Rabinowitz et al. 2002; Hou et al. 2003; Yamashita et al. 2005), as well as cisplatin-ototoxicity (Lopez-Gonzalez et al. 2000; Teranishi et al. 2001; Kalkanis et al. 2004). Protection is dose dependent with higher doses providing the best protection. Increased intake of vitamin E has also been linked to improved hearing outcomes in humans (Spankovich et al. 2011). The best sources of vitamin E include vegetable oils (wheat germ, sunflower, safflower) and nuts (peanuts, hazelnuts, and, especially, almonds) and seeds (sunflower seeds) oils; other oils (corn, soybean) and green vegetables (spinach, broccoli) also provide some vitamin E (National Institutes of Health Office of Dietary Supplements 2010c).

Minerals

Potential roles for several dietary minerals have been suggested.

Magnesium (Mg): Mg supplements reduce NIHL (Scheibe et al. 2000; Haupt & Scheibe 2002; Scheibe et al. 2002; Attias et al. 2003; Haupt et al. 2003); Mg deficient diets increase NIHL (Ising et al. 1982; Joachims et al. 1983; Scheibe et al. 2000). Two double-blind placebo-controlled studies report Mg reduces human NIHL (Joachims et al. 1993; Attias et al. 1994; Attias et al. 2004). However, dietary Mg does not confer protection. Plasma Mg was not reliably correlated with NIHL in male U.S. Army soldiers with exposure (8-18 years) to weapons noise (Walden et al. 2000). Bulgur, oat bran, barley, seeds, beans and spinach are good sources of Mg (US Department of Agriculture 2010).

Selenium (Se): Se was suggested to protect the inner ear given reduced hearing loss in workers with the highest plasma Se levels (Chuang et al. 2007). Brazil nuts, fish, and poultry are good sources of Se (US Department of Agriculture 2010). Other studies have used a synthetic organoselenium compound: ebselen. Several studies demonstrated reduced NIHL with ebselen (Pourbakht & Yamasoba 2003; Lynch et al. 2004; Lynch & Kil 2005; Kil et al. 2007). A Phase I Safety Study using doses of 200-

1600 mg was conducted; 38 % of subjects in each group (placebo, treated) reported adverse events categorized as possibly related to the treatment (Lynch & Kil 2009). The most commonly reported adverse event in both groups was headache. Ebselen is advancing into Phase II efficacy trials (Lynch & Kil 2009).

Copper (Cu), Zinc (Zn), Iron (Fe), and Manganese (Mn): SODs contribute to endogenous defense; they speed destruction of the highly toxic superoxide radical into less toxic free radicals. There are multiple SODs, each with different metal cofactors: Cu and Zn (Cu-Zn-SOD), Fe (Fe-SOD), Mn (Mn-SOD), or Ni (Ni-SOD). Human SOD1 (Cu-Zn-SOD) is found in cytoplasm, human SOD2 (Mn-SOD) is found in mitochondria, and human SOD3 (Cu-Zn-SOD) is extracellular. Genetic variation in human SOD1 (Liu et al. 2010) and SOD 2 (Fortunato et al. 2004; Chang et al. 2009) mediates vulnerability to NIHL in humans, consistent with data from mice that cannot produce SOD1 (Ohlemiller et al. 1999a). With respect to dietary supplements, Fe and Zn have been evaluated. Fe supplement by itself does not appear to influence auditory function; however, Fe in combination gentamicin exacerbates gentamicin-induced hearing damage (in guinea pigs, Conlon & Smith 1998). Zn has also been considered. Zn supplements were recently reported to reduce sudden sensorineural hearing loss in a randomized, placebo-controlled clinical trial (Yang et al. 2011). Tinnitus studies, however, have reported small benefits that are not statistically reliable (Arda et al. 2003), or, no differences (Paaske et al. 1991; Yetiser et al. 2002).

Calcium (Ca), Potassium (K), and Sodium (Na): Ca, K, and Na are critical for endocochlear potential, ion channel regulation, second messenger function, mechanoelectrical transduction, synaptic transmission, and efferent regulation (for recent reviews: Wangemann 2006; Frolenkov 2009). However, there has been practically no research on dietary Ca, K, and/or Na and potential effects on the auditory system. The one exception is the recommendation of low-sodium diets for the treatment of Meniere's disease. It remains the standard of care (Devaiah & Ator 2000; Minor et al. 2004; Gates 2005), even though scientific support is lacking (Thai-Van et al. 2001).

Vitamin/Mineral Combinations

Combinations of antioxidants are appealing given the potential to scavenge multiple free radicals, in multiple cell structures, and also known synergies, such as the observation that vitamin C contributes to the "recycling" of vitamin E. With respect to the auditory system, the combination of □-carotene, vitamins C and E, and Mg has reduced NIHL in animal models (Le Prell et al. 2007a; Tamir et al. 2010; Le Prell et al. 2011a; 2011b). Combinations have also been evaluated in human patients. Reductions in cisplatin-induced hearing loss were reported in cancer patients receiving a combination of vitamins C and E, and Se (Weijl et al. 2004). However, there were no significant differences between placebo and control with respect to hearing loss; significant differences were limited to high frequency hearing loss found when comparisons included only patients with the highest plasma concentrations of the three nutrients. Additional data on dietary supplements come from Takumida and Anniko (2009), who treated elderly patients with a combination of vitamin C, □-lipoic acid, and rebamipide. Enthusiasm for that study is weakened by the lack of a placebo control. Dietary data are difficult to interpret with respect to interactions among nutrients. For example, higher carbohydrate, vitamin C, vitamin E, riboflavin, magnesium and lycopene intakes were all significantly associated with better auditory function, whereas higher cholesterol, fat and retinol intakes were significantly associated with

poorer auditory function (Spankovich et al. 2011). The most important nutrients, and combinations, are yet to be determined.

Flavonoids

Flavonoids are found in fruits, vegetables and beverages such as cocoa, dark chocolate, coffee, green tea, and red wine. Resveratrol is a flavonoid that reduced NIHL in rats (Seidman et al. 2003); resveratrol is found in grape skin and red wine. Scotch whiskey (Koga et al. 2007) and beer hops (Magalhaes et al. 2009) have even greater antioxidant capacity than resveratrol; increases in human plasma antioxidant content after beer are more robust than after wine or whiskey (table 4 in review by Lotito & Frei 2006). However, the potential for health benefits with flavonoids in alcoholic drinks is limited for obvious reasons. Supplements that extract and concentrate the active agents are a more viable option, but efficacy must be established in human clinical trials, and dosing must be optimized. Ferulic acid is another flavonoid that reduces NIHL (Fetoni et al. 2010; 2011). The mechanism of protection of flavonoids is an open question. Robust antioxidant activity has been detected *in vitro*, but flavonoids are poorly absorbed and most of what does get absorbed into the blood stream is rapidly metabolized and excreted (for reviews: Manach et al. 2005; Lotito & Frei 2006). Flavonoid intake increases production of urate (uric acid), which is a potent antioxidant, which may contribute to protection after flavonoid consumption (for review: Lotito & Frei 2006).

Protein

Decreased protein intake increases vulnerability to NIHL (Ohinata et al. 2000), gentamicin (Lautermann et al. 1995a), and cisplatin (Lautermann et al. 1995b). This is not surprising: glutathione production depends on essential amino acids obtained from protein, including glutamic acid, glycine and cysteine. Good sources of protein include poultry, fish, cheese, pork, and beef, followed by milk and yogurt (US Department of Agriculture 2010). When specific amino acids are supplemented, protection against insult is obtained. D-methionine is an amino acid that shows promise as an otoprotective agent (for reviews: Campbell et al. 2007; Campbell & Le Prell 2011; see also ICBEN 2011 paper by Campbell). Another amino acid in protein that has been of interest for protection of the inner ear is cysteine, specifically delivered as N-acetylcysteine (NAC) (for review: Kopke et al. 2007; see also ICBEN 2011 paper by Campbell).

Carbohydrates

Increased risk for hearing loss in adults has been reported for adults with higher glycemic index (carbohydrate quality metric) and glycemic load (metric incorporating both quality and quantify), as well as total carbohydrate intake (Gopinath et al. 2010a). It was not clear if risk was driven more by glycemic index, glycemic load, or total carbohydrate intake. In contrast, Spankovich et al. (2011) reported that higher carbohydrate intake was significantly associated with increased transient evoked otoacoustic emission (TEOAE) amplitude, although carbohydrate intake accounted for only 8 % of the variance (Spankovich et al. 2011).

Fat

Increased dietary fat intake appears to contribute to both cardiovascular disease and hearing loss. After measuring significantly better than expected cardiovascular function and auditory sensitivity in members of the Mabaan tribe of Sudan (Rosen & Olin 1965), Rosen et al. (1970) confirmed a role for dietary fat intake. They manipulated fat intake among patients in two mental institutions in Finland, moving one group off the normal high-fat diet onto a lower-fat experimental diet. Serum cholesterol was significantly lower and hearing thresholds were significantly better in the patients on the low-fat diet after 5 years (Rosen et al. 1970). The diets were then switched at the two institutions; the differences in both serum cholesterol and hearing thresholds were eliminated 3.5 years later, with those on the high-fat diet having worse outcomes than before, and those on the low-fat diet having better outcomes than before (Rosen et al. 1970). Not all fats are equally harmful. Recently, polyunsaturated fatty acids, such as omega-3, were reported to be associated with reduced risk of ARHL in humans (Dullemeijer et al. 2010; Gopinath et al. 2010b). Consistent with this, Spankovich et al. (2011) reported that higher fat intake was significantly associated with poorer TEOAE amplitudes, with fat intake accounting for 8 % of the variance.

Cholesterol

Cholesterol, which circulates in the bloodstream as solid, waxy, fat, is produced endogenously, and it is obtained via diet. Dietary cholesterol increases both low-density lipoproteins (LDL, "bad" cholesterol) and high-density lipoproteins (HDL, "good" cholesterol). LDL and HDL differentially effect cardiovascular health (Institute of Medicine 2005), and perhaps hearing health as well. HDL appears to be beneficial, as deficient HDL levels were associated with increased human hearing loss, although there was no relationship between total cholesterol and hearing loss in that study (Suzuki et al. 2000). High total cholesterol levels have had inconsistent effects across studies. Although Jones & Davis (2000) reported better hearing thresholds in patients with elevated cholesterol levels, Spankovich et al. (2011) reported worse hearing thresholds in subjects that had higher dietary cholesterol. Cholesterol intake accounted for 8 % of the variance in TEOAE amplitude, 30 % of the variance in high frequency PTA (3,000-8,000 Hz), and 21 % of the variance in low frequency PTA (250-2,000 Hz). In some animal models, high cholesterol diets increase the risk for ototoxicity (Pillsbury 1986; Gratton & Wright 1992); however, in guinea pigs fed a high-fat diet for 14 weeks, both body weight and total cholesterol increased, but there was no meaningful change in otoacoustic emission amplitude (Evans et al. 2006).

Caloric intake

Caloric intake is relevant to any discussion of diet and hearing. Data from animal models suggests caloric intake influences susceptibility to ARHL (for recent review: Bielefeld et al. 2010). In brief, experimental animals placed on calorie-restricted (CR) diets (e.g. 25-30 % reduction) have better auditory function and/or improved hair cell survival compared to animals maintained on a standard laboratory diet during aging (for examples: Seidman 2000; Someya et al. 2007, 2010).

CONCLUSIONS

This review focused on the potential impact of dietary choice on hearing health. In most cases, there is minimal data on specific nutrient intake and impact on hearing

and/or hearing loss. The specific interaction between dietary intake and vulnerability to noise is difficult to precisely identify given the complex interactions between diet and vascular health, neural integrity, and biochemical free radical balance, as well as interactions with individual genetics, general health (including medications), and other lifestyle factors. The general conclusions across studies are nonetheless clear. A diet that meets all of the vitamin and mineral recommendations, is low in saturated fats and which contains adequate fiber, is highly recommended. Some higher level supplements may ultimately be shown to be useful for protecting the ear against noise, drugs, or age-related decline, but randomized, placebo-controlled studies are critical to any specific recommendations for supplements.

Clinical studies are underway with several supplements. For example, we are measuring the efficacy of ß-carotene, vitamins C and E, and magnesium, in NCT00808470. D-methionine is being evaluated in NCT01345474. The University of Michigan holds the intellectual property (IP) rights to ß-carotene, vitamins C and E, and magnesium (Miller et al. 2010)[1] and the IP rights to D-methionine are held by Southern Illinois University School of Medicine (Campbell 2001, 2008). The IP rights to ebselen are held by Sound Pharmaceuticals (Kil & Lynch 2010), and clinical trials with that agent are also proposed to be conducted by our team, pending funding. For all of these agents, it will be critical to study dose relationships as many antioxidants have the potential to become pro-oxidants when delivered at high levels (Viña et al. 2007).

NIHL is a compelling occupational problem (for review: May 2000). It is a problem for the military, with tinnitus and hearing loss being the two most prevalent service-connected disabilities for US veterans receiving compensation in fiscal year 2009 (US Department of Veterans Affairs 2010). Finally, a third population worth special note is adolescents and young adults. An increasing prevalence of NIHL in children was suggested given some 12.5 % of US children with notched audiogram configurations (based on a sample of 5249 children, ages 6 to 19 years old, Niskar et al. 2001). There has been significant discussion of whether digital audio player (DAP) devices are potentially hazardous to hearing health. That DAP's can produce harmful sounds levels is clear, but, the extent to which listeners use these devices at levels and durations that can induce hearing loss, and the prevalence of DAP-induced hearing losses in young people as a group, remains under debate (for discussion: editorial comments in Fligor 2006, 2009; Rabinowitz 2010). Male listeners may choose higher listening levels than female listeners (Rice et al. 1987; Williams 2005; Fligor & Ives 2006; Torre 2008; Vogel et al. 2009), and effects of DAP were more evident in males than in females in one recent study (Le Prell et al. 2011c). Taken together, there are multiple populations in need of novel nutraceutical and/or pharmaceutical strategies for protection, and while there is good reason to be encouraged, there is a need for significant additional clinical testing. Until there is clinical data supporting supplement-based strategies, a nutritionally complete, low- saturated fat diet is the best suggestion.

[1] Colleen Le Prell is a co-inventor on U.S. Patent 7,951,845. She previously worked as a paid consultant to OtoMedicine, Inc., and she now serves as the Lead Scientific Advisor for Hearing Health Sciences.

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Oral pharmacologic otoprotective agents to prevent Noise-Induced Hearing Loss (NIHL): When dietary concentration isn't enough

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"DRUGS" VERSUS "NUTRACEUTICALS"

A number of oral pharmacologic protective agents for noise-induced hearing loss are in or approaching clinical trials. The demarcation between a nutraceutical and a drug is not always clear. Broadly, the definition of a drug includes "any chemical substance that affects living processes in a positive or negative manner". However that definition is not the legal or regulatory definition. While each country has its own approval processes, the general approach is frequently similar to that in the United States. In the United States, a molecule or compound is classified as a drug if it is "used to treat or prevent a medical disorder". As a drug, these pharmacologic agents are subject to the Pure Food and Drug act of 1906 requiring a list of ingredients, standards for preparation, registration of dangerous or addictive drugs, and prohibition of false or misleading claims. The Sherley Amendment of 1912 prohibited fraudulent therapeutic claims for patent medications, and the 1938 Federal Food, Drug and Cosmetic Act mandated that drugs could not be sold until they had been tested for safety and all labeling was accurate and complete. In 1951, The Durham Humphrey Amendment specified how drugs could be ordered and dispensed and for the first time limited new drugs to investigational use only. Further, for the first time, a separate category for over the counter (OTC) drugs was specifically created. The OTC classification is designated primarily on the basis of safety. Essentially, OTC drugs are deemed sufficiently safe that they do not need direct medical supervision and can be sold directly to the patient without physician direction. For some drugs both prescription and OTC forms are available with the distinction frequently being in dosing or method of administration. For a review the reader is referred to (Meldrum 2007) Thus agents classified as "drugs" must meet the following standards:

1) The ingredients must be listed.

2) They must meet standards for preparation.

3) They may not make false or misleading claims, including false therapeutic claims.

4) They must be tested for safety.

5) All labeling must be accurate and complete.

6) They are subject to laws regulating how they can be ordered and dispensed.

7) New drugs are limited to investigational use only and cannot be sold until approved by the Food and Drug Administration (FDA).

8) The FDA approval specifies whether the drug is available by prescription only or can also be sold OTC and if so at which dose and in which specific formulation.

The FDA approval is extensive. Current estimates are that, on the average, it takes a drug approximately 15 years and over 1 billion US dollars to go from bench to bedside including FDA approval for marketing.

Thus while expensive and time consuming, an agent classified and FDA approved as a drug affords the consumer many protections and assurances.